

REMARKS

Upon entry of the above amendment, claims 16-32, 34-36, and 38-45 will be pending in the case, claims 33 and 37 having been newly canceled and claims 44 and 45 added. The limitations added to claims 16, 20 and 24 regarding “human”, “humanized”, and/or “chimeric” can be found in claims 22 and 34; further support is found in the specification at page 4, lines 21-27. The limitation of claims 33 and 37 regarding “in vivo” now appears in claims 28 and 35, which are rewritten as independent claims by incorporating the limitations of claim 16, from which they previously depended. Claims 16, 28, and 35 now specify that the fragment is an “antigen-binding” fragment; this is supported, e.g., by the pre-existing limitation in claim 16 that the antibody and fragment “bind to a peptide transporter.” Text is added to claims 20, 22, and 23 to make them consistent with the claims from which they depend, and to clarify the scope. New claims 44 and 45 are supported in the specification at page 9, lines 13-28. No new matter has been added. Applicants submit that the amendments raise no new issues and put the claims into condition for allowance, thereby facilitating prosecution. Entry of the amendments is therefore requested.

Applicants thank the Examiner for the courteous and helpful telephonic interview with the undersigned and her associate, Eugenia Park, on January 7, 2009. During the interview, Applicants discussed proposed amendments substantively similar to those presented above in that they limited the composition claims to antibodies/fragments/diabodies that are human or humanized or (in the case of antibodies) chimeric; reconfigured method claims 28 and 35 as independent, and limited the method claims to *in vivo* methods. The Examiner agreed in the interview that the proposed amendments did not appear to raise any new issues that would preclude their entry at this stage of prosecution. The Examiner suggested that Applicants further amend the claims to specify that the fragment is an “antigen-binding fragment”, in order to avoid a possible rejection for lack of enablement. Applicants appreciate the suggestion, and have followed it in the present amendment.

In the course of the interview, Applicants addressed each of the issues that had been raised in the Final Office Action mailed June 13, 2008. The Examiner asked that the same

points be elaborated in Applicants' written response, to permit his thoughtful consideration. Accordingly, Applicants do so below. The remarks below also include some arguments not touched upon during the interview.

Withdrawal of claims 17, 29, and 39

The Final Office Action stated that Applicants' new claims 16-43 (submitted in the Amendment filed March 5, 2008) had been entered, but claims 17, 29, and 39 were withdrawn as allegedly drawn to a non-elected invention. According to the Final Office Action, "The claims are directed to an antibody that inhibits PMF dependent transport as well as method of using an antibody that inhibits PMF transport and is distinct from PepT1 and PepT2 disclosed in the originally presented claims." Applicants respectfully traverse. Claim 1 as originally presented (now canceled) recited: "An antibody that has ability to inhibit the transport activity of a peptide transporter." While some of the original claims specified that the peptide transporter was PepT1 and/or PepT2, most did not. It therefore cannot be said that Applicants "elected by original presentation" any particular species within the genus of "peptide transporter": if anything, Applicants "elected by original presentation" the entire genus of peptide transporters, as originally presented in claim 1 and as presently represented by claim 16, and are entitled to pursue claims that specify antibodies across the entire genus, as well as those specific for any species or subspecies within that genus. Furthermore, as Applicants pointed out during the interview, claims 17, 29 and 39 specify a class of peptide transporter (a proton motive force (PMF) dependent transporter) that encompasses (i.e., is generic to) PepT1 and PepT2, rather than being "distinct" from them as alleged in the Final Office Action. See, for example, the specification at page 4, lines 9-11. Claims 17, 29 and 39 therefore are intermediate in scope between the broader independent claims (claims 16, 28, and 35) and the narrower claims that specify PepT1 and/or PepT2. It would not be logical, and certainly not consistent with normal unity of invention practice, to require Applicant to pursue the intermediate scope claims in an application separate from both the broader claims and the narrower claims. Applicants therefore ask that the requirement be withdrawn and all pending claims examined.

Obviousness-type Double Patenting

The Final Office Action maintained the provisional rejection for obviousness-type double patenting over the claims 15-39 of co-pending application 10/497,900, applying the rejection to claims 16, 18-22, 28, 30-38 and 40-43 of the present application. Applicants note that application 10/497,900 has not issued, nor even been allowed, so the final scope of the '900 claims cannot be ascertained at this time. Furthermore, Applicants note that the present claims include limitations that are neither disclosed in, nor obvious over, the pending claims of the '900 application. The Examiner has not explained why he believes that the claims of the present application are obvious in view of claims 15-39 of the '900 application. The sole reason of record justifying the rejection is "because the claims of the co-pending application encompass an antibody that binds to PepT1 and or composition comprising an antibody that binds to PepT1 as currently claimed." (Office action dated October 5, 2007, at page 4.) Applicants note that all of the present claims include the limitation "inhibits peptide uptake into a cell expressing the peptide transporter," a limitation that is not obvious in view of the claims of the '900 application. Furthermore, it is not clear why the Examiner believes that the presently claimed methods for inhibiting peptide transporter activity and/or suppressing cell growth are obvious in view of the claims of the '900 application. Clarification, or withdrawal of the rejection, is respectfully requested.

Rejection under 35 USC § 103(a)

Claims 16, 18-28, 30-32, 34-36, 38, and 40-43 were rejected as obvious over Liang et al. (J. Biol. Chem. 1995; 270:6456-6463) or Liu et al. (Biochem. Biophys. Acta 1995; 1235:461-466) in view of Campbell (Monoclonal Antibody Technology; 1984; Elsevier Science Publishing Company Inc.: page 1-33), Winter et al. (Nature 1991; 349:293-299), Basu et al. 1996 or Basu et al. 1998 (previously cited). The rejection is premised on the theory that it is obvious to make monoclonal and humanized antibodies to either PepT1 or PepT2

because it is routine in the art to make monoclonal antibodies to an antigen once it has been cloned and discovered (see Campbell). Moreover, the manipulation of the antibody to make humanized versions of the antibody, antigen binding fragments is also routine in the art (see Winter et al.).

The motivation to make the monoclonal antibodies, according to the Final Office Action at pages 4-5, is simply that the PepT1 and PepT2 antigens were “already known and characterized in the prior art.” Further noting that, “The claims do not specifically indicate that the contacting is performed *in vivo* and therefore the claims read on *in vitro* cellular assays,” the Final Office Action points to Basu et al.’s disclosure of use of polyclonal antibodies in cellular ELISA as rendering the present method claims obvious.

First, Applicants note that claims 33 and 37, which were drawn to the methods of claims 28 and 35, respectively, wherein the cell is *in vivo*, were not rejected as obvious. While not agreeing with the substance of the rejection, Applicants have, in the interest of moving the prosecution to completion, amended claims 28 and 35 to incorporate the “*in vivo*” limitation of claims 33 and 37 (now canceled). Accordingly, all of the present method claims (claims 28-32, 34-36, and 38-45) now specify that the cell is *in vivo* when contacted with the antibody, a scope acknowledged as nonobvious by the Final Office Action. Allowance of these claims is respectfully requested.

With respect to the composition claims, i.e., claims 16-27, Applicants traverse. These claims are presently amended to specify that the antibody is human, humanized or chimeric, and/or the antigen-binding fragment is human or humanized. According to the Final Office Action, “manipulation of the antibody to make humanized versions of the antibody, antigen binding fragments is also routine in the art (see Winter et al.).” However, the Final Office Action does not explain why it would have been obvious to do these “routine” manipulations. As the U.S. Supreme Court reiterated in *KSR v. Teleflex*, 127 S.Ct. 1727, 1741 (2007), a finding of obviousness must be supported by a reason one of ordinary skill would have combined the prior art teachings to first generate a monoclonal antibody with the characteristics specified in the claims, and then to humanize it. Simply being “routine” does not explain why one would bother to invest the time and resources in doing it. Applicants submit that, in the present case, the prior art provided no reason to generate anti-peptide transporter antibodies that inhibit peptide uptake into a cell expressing the peptide transporter, nor even that such antibodies could be produced, and certainly provided no motivation to do the manipulations necessary to humanize them (or make fully human or chimeric versions). Basu et al. teach polyclonal antibodies that bind to PepT1 for use in studying the structure of PepT1, but do not disclose

antibodies (whether polyclonal or monoclonal) that inhibit peptide uptake, and certainly do not teach humanizing such antibodies, or any reason to do so. The purpose for humanizing is to reduce the immune response to the antibody when it is administered to a human, typically where the antibody is utilized as a therapeutic. Absent a proposed therapeutic purpose for an anti-PepT1 antibody that inhibits peptide uptake, there would simply be no logical reason to humanize the antibody. Furthermore, it would be counterproductive to humanize the antibody where the purpose of the antibody is simply *in vitro* studies, as in Basu et al. 1998. Humanizing a monoclonal antibody typically reduces its affinity for its target antigen, so would not be undertaken by any sensible person unless necessary--e.g., to reduce its immunogenicity in a human patient. As explained repeatedly by the U.S. Supreme Court in *KSR v. Teleflex*, the reasons supporting an obviousness rejection must ultimately be based on common sense.

In sum, absent a teaching in the art that

- (a) one should try to generate an anti-peptide transporter monoclonal antibody that inhibits peptide transport by the transporter, *and*
- (b) that one would be successful in generating an antibody with that particular activity, *and*
- (c) that such an antibody should be humanized or chimerized (or generated as a fully human monoclonal antibody to begin with) because there is a potential human therapeutic use for such an inhibitory antibody,

the composition claims as presently amended cannot be deemed obvious. Applicants submit that none of these critical elements has been established by the Final Office Action, much less all of them. In fact, two of the cited references, Liang et al. and Liu et al., if anything *teach away* from a potential therapeutic use for an antibody that inhibits peptide transport by PepT1 or PepT2.

Liang et al. describe the cloning of PepT1. According to the authors,

The pharmacological relevance of this transporter has become evident in recent years because intestinal absorption of orally active amino β -lactam antibiotics and other peptide-like drugs is mediated by this transporter (1-3). It has been proposed that the transporter has the potential to become an important drug delivery system (3).
(page 6456, col.1)

This suggests that it might be therapeutically useful to enhance the activity of PepT1, but certainly not to inhibit it.

Similarly, Liu et al. explain at page 466, col. 1, two other potentially important roles for that peptide transporters (such as PepT1 and PepT2) that function in the kidney: (1) permitting the kidneys to absorb (and thus utilize) peptides from the peptide-based formulas used for parenteral nutrition; and (2) permitting the kidneys to absorb (and thus prevent elimination in the urine) peptidomimetic drugs such as aminocephalosporins, thereby increasing the half-life of these drugs in the circulation. Again, this would suggest that, if anything, one would want to seek a way to increase (not decrease) the activity of PepT1 and/or PepT2 in humans.

Finally, Applicants point out that claims 33 and 37 were not rejected as obvious, an indication that the Examiner acknowledges the nonobviousness of any *in vivo* use of antibodies that inhibit a peptide transporter. If it is not obvious to use the antibodies *in vivo*, it surely cannot be obvious to manipulate the antibodies for the purpose of reducing their immunogenicity in humans. Thus, generating human or humanized or chimeric versions of the claimed antibodies is no more obvious than would be their *in vivo* use.

Withdrawal of the obviousness rejections is respectfully requested.

Claim for foreign priority

At pages 5-6 of the Reply filed March 5, 2008, Applicants asked that the Examiner explicitly acknowledge Applicants' claim for foreign priority by checking the appropriate boxes on the Office Action Summary of the next action. It appears this has not been done in the Final Office Action. Since no issues have been raised by the Office regarding Applicants' claim for foreign priority, Applicants assume this was an inadvertent oversight. Confirmation is respectfully requested.

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CONCLUSION

Applicants submit that the claims are now in condition for allowance. If any issues remain, the Examiner is invited to telephone the undersigned to discuss.

A Request for Continued Prosecution and a petition for extension of time with the necessary fee accompany this Reply. Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

Date: February 19, 2009_____

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